Neurologic Complications of HIV-1 Infection and Its Treatment in the Era of Antiretroviral Therapy

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ABSTRACT

Purpose of Review: Neurologic complications of HIV infection are unfortunately common, even in the era of effective antiretroviral treatment (ART). The consulting neurologist is often asked to distinguish among neurologic deterioration due to opportunistic infection (OI), immune reconstitution, or the effect of the virus itself, and to comment on the role of immunomodulatory agents in patients with HIV infection. Additionally, as successful virologic control has extended the life span of patients with HIV infection, neurologists are called upon to manage long-term complications, such as neurocognitive disorders and peripheral neuropathy.

Recent Findings: Despite the use of ART, significant numbers of patients continue to be affected by HIV-associated neurocognitive disorders, although with milder forms compared to the pre-ART era. Regimens of ART have been ranked according to CNS penetration and are being studied with regard to neuropsychological outcomes. Nucleoside analogs with the greatest potential for peripheral neurotoxicity are no longer considered first-line agents for HIV treatment. Efavirenz, a non-nucleoside reverse transcriptase inhibitor, has the greatest frequency of neurologic side effects among newer ART regimens. The spectrum of clinical manifestations of immune reconstitution inflammatory syndrome (IRIS) continues to grow, including IRIS without underlying OI. A greater understanding of pathophysiology and risk factors has shown that while HIV should be treated early to prevent severe immunocompromise, delayed initiation of ART may be helpful while treating OIs.

Summary: This article reviews the neurologic complications of HIV infection, or its treatment, most commonly encountered by neurologists.

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INTRODUCTION

Since the advent of combination antiretroviral therapy (ART) in 1996, the neurologic complications associated with HIV infection have shifted from those associated with severe immunocompromise, such as opportunistic infections (OIs) of the CNS, to complications related to treatment. Some neurologic complications, such as HIV-associated neurocognitive disorder (HAND), have continued to affect patients despite satisfactory virologic control, although with less severity. This review focuses on these complications that have remained prevalent despite the use of ART, as well as the complications of ART attributable to both medication side effects and immune reconstitution inflammatory syndrome of the CNS (CNS-IRIS).

KEY POINTS

- HIV-associated neurocognitive disorder comprises three entities: asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia.
- The cognitive impairment traditionally associated with HIV infection is that of a subcortical dementia, with difficulties in the speed of information processing and verbal fluency, although this may be changing in the era of antiretroviral therapy.

NEUROLOGIC COMPLICATIONS OF HIV-1 VIRAL INFECTION

HIV-Associated Neurocognitive Disorder

HANDs encompass a range of cognitive impairment from asymptomatic cognitive decline to dementia in patients with HIV infection. HAND is the most prevalent neurologic complication in this population, and as patients continue to live longer on ART, this disabling cognitive disorder is likely to demand greater attention from the neurologic community.

Terminology

Terminology for cognitive change in HIV has previously included HIV encephalopathy, minor cognitive motor disorder, or AIDS dementia complex. Current nosology rates the impairment using neuropsychological testing (if available) or mental status testing and assigns it to one of three categories: asymptomatic neurocognitive impairment, mild neurocognitive disorder (MND), and HIV-associated dementia (HAD).[1] This categorization recognizes the importance of using demographically appropriate means for comparison, as well as the possible contribution from confounding conditions such as depression, opportunistic CNS disease, or coinfection with hepatitis C virus. As the clinical picture of HAND has changed over time, a standardized approach to diagnosis is necessary in order to understand the burden of these disorders. The recognition of asymptomatic neurocognitive impairment requires detailed neuropsychological testing, which is not readily available in some clinical settings. A screening test such as the Memorial-Sloan Kettering scale or 2007 consensus Frascati rating can be used to determine whether patients need further neuropsychological testing.[2]

Clinical Features

Asymptomatic neurocognitive impairment is characterized by poor performance in two or more domains on neuropsychological or mental status testing in patients who do not report or otherwise demonstrate cognitive decline. These patients may go on to develop symptomatic impairment (MND or HAD), but the time course of cognitive change in HIV is not predictable or linear in many cases. Even with consistent treatment with ART, cognitive performance may fluctuate over time, making diagnosis more difficult; in some cases complete recovery occurs after initiation of ART.[3] Patients with MND report or demonstrate mild functional decline not explained by a confounding condition, and on neuropsychological or mental status testing perform at least one SD below an appropriate normative mean in at least two cognitive domains. These patients are likely to be able to continue working, although at a reduced level of productivity or efficiency. Movement disorders, such as gait disturbance, tremor, and impairment of fine manual dexterity, may be present.[4] HAD describes a pattern of cognitive loss greater than two SDs below the mean in at least two cognitive domains (**Case 4-1**). With great impairment in daily function, these patients are unlikely to be able to live independently.

The cognitive impairment classically described in HIV infection is a subcortical dementia, more similar to the cognitive deficits seen in Parkinson or Huntington disease than the cortical dementia of Alzheimer disease. Preferentially affecting the fronto-striato-thalamo-cortical circuits, patients with HIV infection have traditionally been found to have greater difficulty in abstraction, rapid information processing, verbal fluency, decision making, and maintaining working memory.[5] Prospective memory has been demonstrated to be impaired in HIV; this type of memory, called ''remembering to remember,'' is critical to intentional and planning

Case 4-1

A 56-year-old man with known HIV infection of 2 years' duration was brought to the hospital by his brother, who reported that the patient was not acting like himself and was quieter than usual. The patient had been lost to follow-up after a prolonged hospitalization in which he was found to have HIV/AIDS (CD4+ T-cell count of 6). His brother stated that they had recently moved to a new apartment and that the patient was unable to determine how to unpack the boxes or put away his belongings. He had little spontaneous speech, inattention, apathy, disorientation to time, and 0/3 recall at 3 minutes. He had mild retropulsion, decreased arm swing, a broad-based gait, and decreased sensation to temperature and vibration in a length-dependent, stocking-glove pattern, with positive sway on Romberg testing.

MRI of the brain showed a symmetric leukoencephalopathy and generalized cerebral atrophy (**Figure 4-1**). Lumbar puncture showed a white blood cell (WBC) count of 2/μL and normal protein and glucose concentration; infectious studies for cryptococcal antigen, JC virus, Epstein-Barr virus, and cytomegalovirus were negative by PCR. Serum antibody testing was negative for hepatitis B and C viruses; vitamin B_{12} level was 650 pg/mL, and rapid plasma reagin was nonreactive. The CD4+ T-cell count was 0 cells/μL, and the HIV viral load was 286,270 RNA copies/μL. HIV genotyping indicated possible resistance to saquinavir and ritonavir, likely consistent with poor medication adherence.

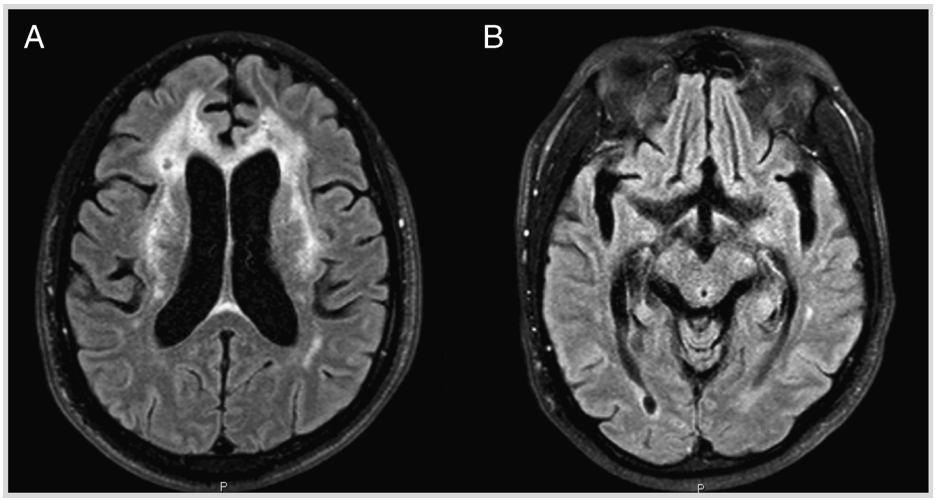

FIGURE 4-1 Fluid-attenuated inversion recovery sequence of MRI shows hydrocephalus *ex vacuo*, diffuse leukoencephalopathy (*A*), and diffuse, generalized atrophy (*B*). This degree of leukoencephalopathy is not a cardinal imaging feature of HIV encephalopathy but is commonly found in patients with advanced HIV infection and likely represents axonal injury.

Comment. At the time of hospitalization for personality change, the patient met criteria for HAD as he had significant cognitive loss with multiple domains affected, particularly psychomotor speed and executive function, and was unable to live independently. While his ventricles were enlarged on MRI, he had no urinary symptoms and a large volume lumbar puncture resulted in no improvement of his gait. After re-initiating treatment with ART and OI prophylaxis, he showed some improvement in his independent function on a visit more than 6 months later, as evidenced by regular checks of his pillboxes to ensure that he was filling them properly and adhering to his regimen.

tasks such as remembering to take daily medications.[6] Memory domains reliant on posterior neocortical and temporolimbic systems, such as object naming and memory consolidation, were traditionally thought to be spared in HIV-infected individuals,[5] although evidence suggests that the cognitive domains affected may be changing in the era of ART.[7] The large National Institute

KEY POINTS

- The use of antiretroviral therapy has decreased the prevalence of the most severe dementia associated with HIV, but the milder forms of HIV-associated neurocognitive disorder have remained highly prevalent.
- Low CD4+ T-cell nadir continues to be a significant risk factor for the development of HIV-associated neurocognitive disorder in the era of antiretroviral therapy.
- The primary goal in management of HIV-associated neurocognitive disorder is to prevent HIV replication in the CNS.

on Mental Health cohort CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study used standardized neuropsychological tests to evaluate 857 patients from 1988 to 1995, and 937 patients from 2000 to 2007. Between the pre-ART and ART eras, fewer patients performed poorly in verbal fluency (eg, number of animals named in timed setting), speed of information processing (digit vigilance time), and motor domains (grooved pegboard test), while more patients showed deficits in learning and memory (story memory test) and executive functioning (Wisconsin card-sorting test). The domains of recall, working memory, and attention were stable across the two time periods.[7] This shift in cognitive domains most affected in patients with HIV infection has important implications for trials of adjunctive therapy, such as antioxidants or neuroprotective agents, in determining which cognitive tests to study. Whether these data reveal a greater degree of cortical impairment, rather than subcortical pathology, in HAND in the era of ART will require neuroimaging and neuropathologic correlation.

Epidemiology

Prior to the introduction of combination ART in 1996, dementia in patients with HIV infection was described as a consequence of profound immunosuppression as reflected by the CD4 nadir.[8] The number of HIV-infected patients with moderate to severe dementia has been dramatically reduced by the use of ART, with one study describing a decrease in incidence from 7% in 1989 to 1% in 2000.[9] In patients with sustained virologic control, however, the continued prevalence of the milder subtypes of HAND has led to the question of whether neurocognitive decline could be treatment resistant in some patients. In the CHARTER study, despite a significant decrease in HAD from rates reported in the pre-ART era, 45% of patients had neuropsychological impairment diagnosed either as asymptomatic neurocognitive impairment (33%) or MND (12%).[10] Low CD4+ T-cell count nadir has continued to be a risk factor for the development of HAND in the era of ART, suggesting that severe immunosuppression may lead to irreversible brain pathology.[7] Alternatively, the brain may act as a reservoir for HIV replication due to variable blood-brain barrier penetration by ART as well as viral sequestration in CNS macrophages.[11]

Despite the decline of the most severe HAND, HAD, cognitive disorders in HIV remain a significant source of morbidity for patients in the United States and elsewhere. While the degree of cognitive impairment may be milder in patients with HAND in the ART era, these ''mild'' or ''minor'' cognitive syndromes have nonetheless been associated with low antiretroviral adherence and thus represent a significant risk factor for decreased survival.[12]

Management

As HAND has been shown to directly correlate with CD4 nadir, the primary goal in management of HAND is to prevent HIV viral replication in the CNS. In evaluating the efficacy of new ART agents, however, demonstrating the penetration of any drug into brain parenchyma is challenging. CSF drug levels are used as a proxy of CNS penetration, but the relationship of CSF to brain levels is unknown. The difficulty of achieving satisfactory CSF levels is a well-recognized problem, as plasma drug levels are usually much higher than those in the CSF, and protein pumps such as P-glycoprotein may eliminate protease inhibitors from the brain. Macrophages, the primary target of HIV in the brain, require much higher concentrations of antiretrovirals for effective control of viral replication than that

required by T lymphocytes.[13] Additionally, resistance mutations in the virus can differ between the CSF and plasma, contributing to the potential reservoir of viral replication in the CNS.[14]

Previously, guidelines from the US Department of Health and Human Services (DHHS) regarding antiretroviral use in adults recommended initiation of ART in patients with a history of an AIDS-defining illness or CD4+ T-cell count less than 350 cells/μL; while HIV-related encephalopathy is listed on the Center for Disease Control and Prevention guidelines as an AIDS-defining illness, HAND has not been specifically addressed. The 2012 DHHS Guidelines for HIV Treatment now recommend ART for all HIV-infected patients regardless of CD4+ T-cell counts.[15] Given the difficulty in ensuring CNS penetration and that higher levels are required to control replication in brain macrophages, early initiation of ART in patients with neurocognitive abnormalities is paramount.

Regimens associated with better CNS penetration. A CNS penetration-effectiveness (CPE) index recently has been proposed to guide the choice of antiretrovirals in patients with HAND. Each antiretroviral drug is given a score of 1 to 4 (4 = much above average CNS penetration, 3 = above average, 2 = average, 1 = below average), and the sum of the individual agents' scores in a combination regimen provides the CPE score for that regimen. Individual ART agents with scores of 4 include zidovudine, nevirapine, and indinavir/ritonavir.[16] While ART regimens with higher CPE scores have been shown to correlate with improved CSF viral suppression, in one study patients on higher CPE-scoring regimens also demonstrated poorer neuropsychological performance, raising the possibility that some drugs may be neurotoxic.[17] Similar studies have shown improved performance on neuropsychological testing with better CNS penetration of ARTs[18] or no effect.[19] A multicenter, randomized, single blind trial is currently recruiting participants in order to compare ART regimens of different CNS penetration with the primary outcome measurement of neuropsychological testing after 16 weeks of treatment.[20]

Other agents. Because of concern that HAND may be resistant to effective virologic control, a number of agents have been tested in previous or ongoing trials with regard to controlling inflammation in the brain or providing neuroprotection. Trials have included memantine, nimodipine, selegiline, minocycline, atorvastatin, lithium, valproic acid, and selective serotonin reuptake inhibitors (SSRIs), such as citalopram.[21] Some agents have shown benefits on biomarkers of neurotoxicity, such as brain levels of *N*-acetylaspartate in magnetic resonance spectroscopy, or clinical benefit in smaller studies; but larger studies with adequate power have not yielded positive results for these adjunctive agents. Evidence from small studies, however, and pharmacologic mechanisms support the continued investigation of psychiatric medications such as SSRIs and glycogen synthase kinase 3-β inhibitors, as well as antioxidants, in reducing inflammation or other toxic effects of HIV replication in the brain.[22]

KEY POINT

- The CNS penetration-effectiveness index ranks each antiretroviral agent compared to ''average'' CNS penetration.

Other CNS Syndromes Associated With HIV Infection

In some patients with HIV infection, the viral infection presents with a multiple sclerosis–like syndrome with either a relapsing-remitting or a progressive, fulminant course, correlating with leukoencephalopathy on MRI.[23] Pathology in these patients is consistent with demyelination but without identification of JC virus or the pathologic changes characteristic of progressive multifocal leukoencephalopathy (PML). A syndrome of fulminant encephalopathy,

frequently accompanied by renal failure and seizures, has been identified in HIV-infected patients using IV drugs (**Case 4-2**).[24] These patients invariably have T2-signal abnormalities in the bilateral basal ganglia and occasionally also present with movement disorders. In HIV-infected children, basal ganglia calcification is a common finding among patients with abnormal imaging.[25] These patients almost uniformly have developmental delay.

Case 4-2

A 51-year-old woman with HIV infection of at least 3 years' duration presented to the emergency department with dizziness. In the weeks prior to admission she was frequently using cocaine and heroin, and both drugs were found in her urine. She had been noncompliant with ART, and her CD4+ T-cell count was 5 cells/μL with HIV viral load of 209,374 copies/mL. She had an encephalopathy and a shuffling gait with postural instability. CSF showed 0 WBCs but elevated protein concentration (76 mg/dL). She was found to be in acute renal failure with a serum creatinine level of 1.1 mg/dL. Bacterial, fungal, and mycobacterial cultures from the CSF were negative, as were toxoplasma antibodies, Venereal Disease Research Laboratory testing, cryptococcal antigen, and PCRs for Epstein-Barr virus, JC virus, herpes simplex virus type 1 and type 2, cytomegalovirus, varicella-zoster virus (VZV), and arboviruses. MRI of the brain showed diffuse hyperintense T2/fluid-attenuated inversion recovery (FLAIR) signal abnormalities in the bilateral basal ganglia and periventricular white matter (**Figure 4-2**). Despite supportive care, her mental status deteriorated over the following 6 months and she died.

Comment. A syndrome of acute encephalopathy and renal dysfunction, frequently accompanied by seizures and often progressing rapidly to death, has been described in HIV-infected drug abusers with poor virologic control.[24] CSF is typically acellular with elevated protein concentration. Even though the basal ganglia are frequently affected in HIV infection and show atrophy in HAND and calcification in perinatally acquired HIV infection, this syndrome of fulminant encephalopathy in HIV-infected drug abusers shows very characteristic diffuse, bilateral basal ganglia abnormalities on T2/FLAIR imaging. Two patients who survived had received antiretroviral therapy during admission, suggesting a possible neuroprotective effect of ART in these cases.

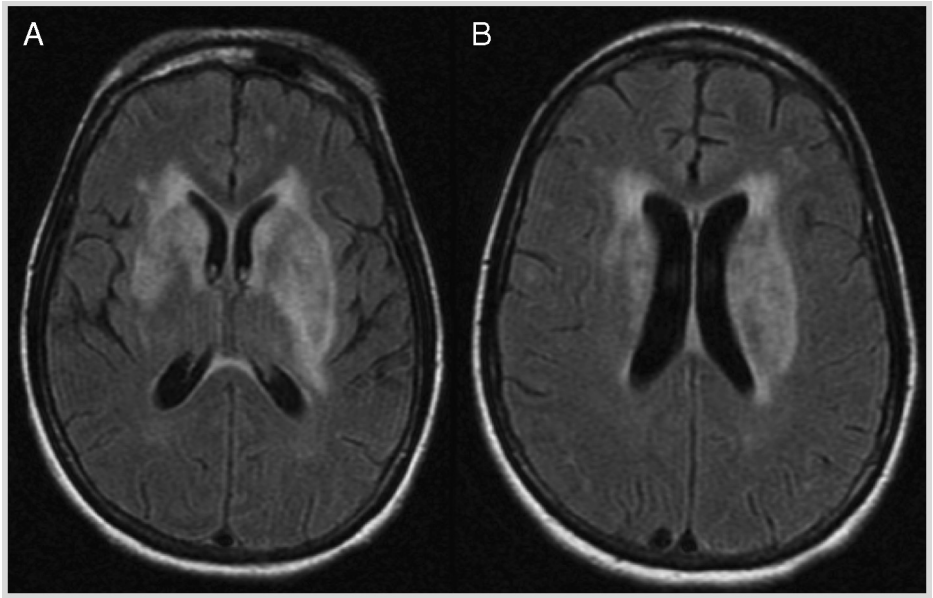

FIGURE 4-2 Fluid-attenuated inversion recovery sequence of MRI shows diffuse bilateral hyperintense signal in the basal ganglia (*A*) and periventricular white matter (*B*).

HIV-ASSOCIATED DISTAL SYMMETRIC POLYNEUROPATHY

HIV infection has been associated with numerous syndromes in the peripheral nervous system, most commonly a distal symmetric polyneuropathy. Peripheral neuropathy in patients with HIV infection may be related to neurotoxic ART (antiretroviral toxic neuropathy [HIV-ATN]) or to the viral infection itself (HIV distal sensory polyneuropathy [HIV-DSP]). While the neurotoxicity of certain antiretrovirals has led to declining use in favor of other agents, many patients alive today have been on numerous therapeutic regimens and thus may continue to be affected by irreversible peripheral neuropathy.

Epidemiology

In the era preceding ART, HIV-DSP was associated with profound immunosuppression. Peak HIV viral load and CD4+ T-cell nadir were found to be risk factors for the development of HIV-DSP and also correlated with the severity of symptoms.[26] In studies comparing rates of HIV-DSP in cohorts studied before and after the introduction of ART, the prevalence of HIV-DSP is quite similar: 55% of pre-ART patients affected in the Dana cohort[27] and 53% of post-ART patients affected in the Manhattan HIV Brain Bank.[28] In the studies of HIV-DSP in patients in the ART era, the degree of immunosuppression no longer predicts the development or the severity of neuropathy.[28] Similar to the theory for the continued prevalence of HAND despite better virologic control, the continued prevalence of HIV-DSP may reflect low levels of viral replication or subsequent chronic inflammation that are below the level of detection and yet sufficient to cause neurotoxicity. Another theory for the persistence of HIV-DSP is an immune reconstitution mechanism of damage to peripheral nerves. With longer life spans, patients with HIV infection are at greater risk for other medication-induced (and illicit drug–induced) neurotoxicity and other conditions, such as diabetes, that lead to peripheral neuropathy. These additional risk factors have been shown to contribute to HIV-DSP.[28]

Clinical Features and Management

HIV-DSP, a small fiber sensory neuropathy, typically manifests as painful paresthesia or painless numbness in the feet. While symptoms may spread during weeks to months, symptoms in HIV-DSP are typically confined to the lower extremities below the knees, with loss of deep tendon reflexes at the ankles. Painful paresthesia is common in this syndrome; in one study of 100 patients screened during 2 weeks in Australia, 42% of patients had a distal sensory neuropathy, and of these, 93% reported painful symptoms.[29] As a small fiber sensory neuropathy, pathologic changes may be absent on EMG and nerve conduction studies, thus requiring skin biopsy for definitive diagnosis. In most cases, classic symptoms in the appropriate clinical context are sufficient to formulate a diagnosis and treatment plan.

Given that many patients with HIV-DSP would be otherwise healthy, with their HIV well controlled on ART, these painful symptoms have a significant impact on quality of life. Lamotrigine has shown benefit in treating painful HIV-DSP in one randomized controlled trial in patients previously exposed to neurotoxic ART, although this benefit was only seen in a secondary outcome measure using a visual analog scale.[30] Other agents traditionally used to treat neuropathic pain, such as amitriptyline, pregabalin, and gabapentin, have not shown efficacy in treating painful HIV-DSP in large randomized controlled trials.[31] Mixed data exist for agents such as

KEY POINTS

- Distal sensory polyneuropathy is the most common neurologic manifestation of HIV infection and remains highly prevalent despite the use of antiretroviral therapy.
- Neuropathic pain is a common finding in HIV distal sensory polyneuropathy. Agents traditionally used to treat neuropathic pain are frequently used, although none has shown benefit in randomized controlled trials of painful HIV distal sensory polyneuropathy.

KEY POINTS

- Peripheral neuropathy is most commonly associated with the ''d drugs'' among nucleoside analogs, such as didanosine, stavudine, and zalcitabine. These medications are now rarely used as first-line agents when other options exist.
- More than 50% of patients on efavirenz experience neurologic side effects, usually limited to the first month or weeks of treatment.

high concentration topical capsaicin. Injections of recombinant human nerve growth factor have shown potential for benefit in studies, although this agent is not yet approved by the US Food and Drug Administration. Smoked cannabis has been shown to effectively control pain in HIV-DSP but cannot be recommended for routine therapy as the mental side effects are disturbing for some, preparations are not standardized, and long-term risks of lung cancer are associated with inhalation of cannabinoids.[31]

NEUROLOGIC COMPLICATIONS OF TREATMENT FOR HIV

While HIV has morphed from a rapidly fatal infection into a chronic, treatable disease because of the efficacy of ART, the range of possible complications related to immune recovery, rather than immune deficiency, continues to grow. Additionally, side effects of chronic treatment with ART, such as peripheral neuropathy, are gaining in importance as patients live longer and the cumulative toxicity over time is greater.

NEUROLOGIC SIDE EFFECTS OF ANTIRETROVIRAL THERAPY

Neurologists are unlikely to be prescribers of ART, yet the neurologic side effect profiles of these medications are likely relevant to the consulting neurologist. Side effects of ART therapy are frequently in the differential diagnosis of neurologic presentations of patients with HIV infection, such as the patient with acute mental status change after initiating therapy, or patients on chronic ART with peripheral neuropathy.

Nucleoside Analogs

The potential of any nucleoside reverse transcriptase inhibitor to cause peripheral neuropathy is directly related to the mitochondrial toxicity of the specific agent. Dideoxynucleoside agents (''d drugs'') such as didanosine (ddI), stavudine (d4T), and zalcitabine (ddC) are therefore considered among the most peripheral neurotoxic agents and rarely used as first-line agents when other options exist. Combination therapy with didanosine and stavudine is especially avoided.[32] HIV-ATN usually appears 2 to 3 months after initiation of treatment and may be more likely to affect the hands earlier than would be expected in HIV-DSP. The time course may be most helpful in distinguishing HIV-ATN from HIV-DSP, as these two entities cannot be differentiated electrophysiologically.[33] Stavudine has also been associated with a neuromuscular syndrome of acute, progressive ascending weakness, similar to Guillain-Barré syndrome. This HIV-associated neuromuscular weakness syndrome (HANWS) usually includes lactic acidosis and hepatomegaly, invoking mitochondrial toxicity in its pathogenesis, although it has been reported at a delay (up to 90 days) after discontinuation of ART.[34]

Non-nucleoside Reverse Transcriptase Inhibitors

Of the non-nucleoside reverse transcriptase inhibitors, efavirenz is most commonly associated with neurotoxicity, characterized by specific neuropsychiatric symptoms that occur in more than 50% of patients on the medication. Typically occurring at the onset of efavirenz use, the patient may experience vivid dreams or nightmares, headaches, or psychiatric phenomena such as dissociative symptoms, depression, anxiety, or more rarely paranoia or psychosis. However, these symptoms abate within 1 month of treatment.[35]

Protease Inhibitors

One study of patients on protease inhibitors between 1998 and 2004 suggested a link between these agents and the development of peripheral neuropathy.[36] The early data regarding the

possible peripheral neurotoxicity of protease inhibitors are complicated by the fact that many of the patients reported were also likely exposed to nucleoside reverse transcriptase inhibitors, such as stavudine, and that the specific protease inhibitors implicated are no longer among the first-line ART agents. A much larger study of 1159 patients with HIV infection found no increased risk for neuropathy associated with protease inhibitor use after adjusting for other risk factors.[37]

COADMINISTRATION OF ANTIEPILEPTIC AND ANTIRETROVIRAL MEDICATIONS

Recently, a joint panel of the American Academy of Neurology and the International League Against Epilepsy issued guidelines for treatment of seizures in patients with HIV infection.[38] Given the high comorbidity of these conditions as well as the greater availability worldwide of antiepileptics that are enzyme inducers, these guidelines help neurologists in making appropriate adjustments to maximize therapeutic efficacy of antiepileptic drug–ART regimens.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

IRIS is the phenomenon of clinical deterioration despite immune recovery from an immunodeficient state. Since the first report of acute *Mycobacterium avium-intracellulare* infection in a patient with HIV-1 infection treated with zidovudine in 1992,[39] there has been ongoing research regarding the pathophysiology of the detrimental immune response in IRIS as well as the range of associated infections and clinical manifestations. While CNS-IRIS in HIV is most frequently linked to *Cryptococcus* or PML, other pathogens are continuing to be reported in association with CNS-IRIS after ART administration. Clinical deterioration despite effective virologic control on ART can also occur without an identifiable pathogen, such as in the acute syndrome of fulminant HIV encephalitis after ART. While IRIS can affect any organ system, this review focuses on IRIS in the CNS in the context of HIV infection.

Terminology

When IRIS is related to an OI, it is typically categorized in the literature as ''unmasked'' IRIS versus ''paradoxic'' IRIS. In unmasked IRIS, the immune-suppressed individual is already known to have an OI but is unable to mount an immune response against it. Once ART is initiated, the recovering immune system produces a robust immune response against the pathogen, but the inflammation thus produced is clinically detrimental to the patient. In paradoxic IRIS, the patient has been treated for an OI but suffers a clinical relapse once ART is initiated. These terms can be confusing since all IRIS is paradoxic in the sense that immune recovery, not immune deficiency, produces the characteristic clinical worsening in these patients; similarly, whether an infection has been treated or untreated, it is revealed (or unmasked) by the process of immune reconstitution. We prefer terms that describe the temporal course of the OI with regard to IRIS: ''simultaneous'' IRIS when the OI and IRIS clinically manifest at the same time in a patient, and ''delayed'' IRIS when IRIS follows initiation of ART in a patient known to be infected with an opportunistic pathogen.

Epidemiology and Risk Factors

While IRIS in any organ system may complicate ART initiation in as many as one-third of patients with HIV infection,[40] CNS-IRIS is much rarer, occurring in only 1% of patients after starting ART.[41] The major risk factors identified for the development of CNS-IRIS are the degree of immunosuppression

KEY POINTS

- Guidelines are available for using the combination of antiretroviral and antiepileptic medications; drug levels may be significantly altered depending on which medications are used together.
- Immune reconstitution inflammatory syndrome is characterized by clinical deterioration despite immune recovery from deficiency.

KEY POINT

- Risk factors for the development of CNS immune reconstitution inflammatory syndrome are a low CD4+ T-cell nadir, the presence of an underlying opportunistic infection, and the rapid rate of decline in the HIV viral load.

at the time of ART initiation as reflected by CD4+ T-cell nadir, the presence of any underlying OI, and the rate of immune recovery as demonstrated by precipitous decline in viral load after starting ART.[42] In one study, the incidence of CNS-IRIS rose from 0.9% of all HIV-infected patients starting ART to 1.5% in those with CD4+ nadir less than 200 cells/μL.[41] Since patients in resource-limited settings may only receive ART once they present with an AIDS-defining illness, it may be that CNS-IRIS rates are actually higher worldwide. Genetic factors are likely also relevant as some patients with severe immunosuppression and rapid immune recovery do not develop IRIS. Expression of proinflammatory cytokines such as interleukin (IL)-6, as well as certain cytokine polymorphisms such as tumor necrosis factor α-308*2, may be greater in the subpopulation of HIV-infected patients who develop IRIS.[43,44] Additionally, an anti-inflammatory cytokine polymorphism in the IL-12B gene has been negatively associated with non-CNS herpes-associated IRIS.[44]

Pathophysiology

Given the range of IRIS cases reported in the literature, the picture that has emerged is not of a unifying IRIS physiology but rather a myriad of diverse clinical, radiologic, and immunologic syndromes that likely encompass multiple disease mechanisms. What unifies these cases is the trafficking of activated lymphocytes into the brain. It is unclear why some patients are more likely than others to develop IRIS during immune reconstitution. Several studies of immunologic profiling have shown that IRIS patients had greater numbers of activated CD4+ T cells of the effector memory subtype[45] with increased expression of interferon-γ[46] and programmed-death molecule 1 (PD-1) prior to ART initiation, suggesting that they are primed for immune activation.[47] While PD-1 expression has been linked to failure of immune restoration in ART and T-cell exhaustion,[47] its presence in patients with IRIS may imply a disordered process of immune restoration. The abnormal presence of activated lymphocytes in the brain may also occur on a chronic basis in HAND that develops despite adequate virologic control.[10]

After initiating ART in the patient with HIV infection, immune reconstitution occurs in a biphasic manner. First, memory T cells increase in concert with thymic production of naïve T cells. Secondary lymphoid organs that may have been damaged because of HIV-mediated inflammation begin to recover and contribute to the rising numbers of CD4+ T cells by releasing these, usually within 3 to 6 months of ART initiation.[48] CD8+ T cells may increase more rapidly and thus may be a better indicator of early risk for IRIS than CD4+ T-cell counts alone; CD8+ T-cell levels tend to return to baseline after 4 months of ART, while CD4+ T cells undergo a more gradual and longer-lasting increase.[49,50] Patients with IRIS have higher numbers of activated effector memory CD4+ T cells and lower numbers of naïve CD4+ T cells and central memory CD8+ T cells.[45] The long-term outcome of patients who recover from IRIS is unknown, but autopsy studies show that the inflammatory infiltrates associated with opportunistic infections consist of large numbers of HIV-infected cells. Hence the possibility exists that they may establish a reservoir in the brain with long-term sequelae.

Opportunistic Infection

The spectrum of viral, bacterial, fungal, and parasitic OIs, well described for their catastrophic consequences for patients with HIV infection prior to the advent of ART, have now been associated with IRIS. When an underlying infection is present, initiating

ART in a patient with HIV infection causes a rise in the circulating T-cell population, which may lead to an enhanced or severe inflammatory response to the infection. The clinical manifestations of CNS-IRIS, as well as in the latency of symptom onset after ART, vary significantly depending on the OI precipitating the immune response. This suggests that while all CNS-IRIS may share general phenomena, such as blood-brain barrier breakdown and leukocyte infiltration, pathogen-specific disease mechanisms may be responsible for IRIS seen in the context of each OI.

Viral Pathogens

JC Virus. Spread of the JC virus, a ubiquitous polyoma virus, to the glia in immunosuppressed patients may lead to development of PML, a frequently devastating disease characterized by profound destruction of the white matter and rapidly progressive neurologic decline corresponding to the brain lesions. As no antiviral is available for JC virus, PML is only treatable in the context of HIV, since ART may enable the immune system to recover from the viral infection; however, these patients are subsequently at risk for PML-IRIS. Of approximately 5% of HIV-infected patients who develop PML, 19% may develop PML-IRIS after beginning treatment with ART.[51] The development of IRIS in the HIV-infected patient with PML can at times present a diagnostic challenge. While some patients develop contrast enhancement of the white matter lesions on MRI, in others the enhancement may be subtle. The uptake of gadolinium in these lesions is associated with predominantly CD8+ T cells infiltrating the perivascular spaces and in some cases the parenchyma, macrophages, and CD4+ T cells.[52] Additionally, significant neurologic deficits, such as aphasia and apraxia, associated with PML in the HIV-infected patient may make detection of any further clinical deterioration after initiation of ART quite difficult. PML-IRIS typically develops within 4 to 8 weeks after the initiation of ART but has been reported to occur as late as 2 years.[53] The mortality rate may be 42% or higher in PML-IRIS,[54] with a worse prognosis associated with HIV-infected patients diagnosed first with PML and subsequently developing PML-IRIS after initiation of ART.[55] Clinical response to steroids confirms the diagnosis of PML-IRIS, as steroids will have no effect on PML but will help control the inflammatory response and frequently produce some clinical improvement in PML-IRIS.[55]

Herpes viruses. Multiple viruses from the Herpesviridae family have been described as the underlying OI in CNS-IRIS. VZV is the causative agent of varicella (chicken pox) and herpes zoster (shingles) with a prevalence above 90% in adults.[56] A ubiquitous latent virus, VZV remains dormant in the dorsal root ganglia after the primary infection characterized by fever and vesicular rash. Clinical syndromes resulting from reactivation of VZV in the immunocompetent patient may range from painful dermatomal rash (zoster) to transverse myelitis, but in the immunocompromised patient also include encephalitis and vasculitis, which may lead to cerebral infarcts. VZV-IRIS has been described as presenting 4 to 10 months after the initiation of ART and manifesting clinically as encephalitis and vasculitis leading to cerebral infarcts.[57] In one report, the VZV-IRIS was not controlled by acyclovir alone but required concurrent acyclovir and corticosteroids.[57] Cytomegalovirus has also been associated with IRIS in patients with HIV infection, although it typically manifests as retinitis and only rarely as CNS-IRIS. These few cases of CNS-IRIS presented as ventriculitis and polyradiculopathy and responded to treatment with ganciclovir with or without foscarnet.[58] One case of Epstein-Barr

KEY POINTS

- Progressive multifocal leukoencephalopathy CNS immune reconstitution inflammatory syndrome frequently presents with enhancement of the white matter lesions on MRI, and immunomodulatory therapy may be required.
- Varicella-zoster virus CNS immune reconstitution inflammatory syndrome may present with encephalitis or cerebral vasculitis leading to infarcts.

KEY POINTS

- *Cryptococcus* is the most common fungal infection in immune reconstitution inflammatory syndrome. A longer range of latency, the clinical manifestation of meningitis only, and a delay in the normalization of the cryptococcal antigen after treatment may contribute to difficulty in diagnosis and treatment.
- Clinical deterioration is common with the initiation of treatment for tuberculosis but can occur much later in the CNS than in other organ systems.

virus CNS-IRIS is reported with the manifestation of vision loss 6 weeks after ART, with corresponding T2/FLAIR hyperintensities in the optic chiasm and Epstein-Barr virus detected in the CSF by PCR, without recovery of vision. Herpes simplex virus is suspected to have caused temporal lobe encephalitis in one report of CNS-IRIS that responded to acyclovir, although the pathogen could not be found in the CSF by PCR.[59]

Fungal Pathogens

Cryptococcus neoformans is the most common fungal infection associated with CNS-IRIS.[60] Cryptococcal infections may be associated with 10% to 30% of all CNS-IRIS,[53] most often clinically manifest as aseptic recurrence of prior meningitis and rarely as intracranial cryptococcoma.

Several factors may make the diagnosis of cryptococcal CNS-IRIS challenging. Cryptococcal CNS-IRIS has a longer range of possible latency of onset than that associated with PML or tuberculosis. While typically presenting 3 to 20 months after the initiation of ART, it has been reported as soon as 14 days and as long as 2 years after starting ART.[61] The clinical manifestations of cryptococcal CNS-IRIS can be difficult to detect as the acute development of aseptic meningitis may be mistaken for postinfectious hydrocephalus; both are characterized by headache, nausea, and vomiting. Additionally, because tests for the cryptococcal antigen remain positive for several months after adequate treatment at slowly decreasing dilutions, the possibility of cryptococcal CNS-IRIS should be considered if sterile inflammation of the CSF is present and no viable yeast is found in culture. Neuroimaging shows new meningeal or choroid plexus enhancement or perivascular enhancement in the sulci, indicating a cellular immune response to the underlying infection.[62] HIV-infected patients with cryptococcal CNS-IRIS compared to non-IRIS cryptococcal meningitis most often have higher opening pressures, CSF white cell counts, and glucose concentrations.[40]

One case has been reported of *Candida* sp meningitis with acute deterioration after initiating treatment with ART. This patient, who presented with subacute meningitis during a period of noncompliance with ART, rapidly succumbed despite ART initiation and evidence of improved immune function. Postmortem examination revealed basilar *Candida* sp meningitis as well as CD8+ T-cell perivascular infiltrates, particularly in the brainstem.[63]

Bacterial Pathogens

Antituberculous therapy has been recognized for its potential to cause clinical deterioration, long before the era of ART. Mycobacterial CNS-IRIS typically presents 5 to 10 months after ART initiation, most commonly with *Mycobacterium tuberculosis* manifesting tuberculosis meningitis and rarely as tuberculoma.[64,65] Because mycobacterial CNS-IRIS occurs much later than mycobacterial IRIS in other organ systems, and also because of the difficulty of establishing a diagnosis in tuberculous meningitis, the prevalence of mycobacterial CNS-IRIS is unknown. While cases of clinical deterioration after ART initiation due to expansion of intracranial tuberculomas have been described,[64] fewer reports are available regarding CNS-IRIS with recrudescence or development of tuberculous meningitis. According to one study, as many as 21% of patients in South Africa have developed *Mycobacterium*-related CNS-IRIS.[60] Given that one-third of the world's population has been infected with tuberculosis, a greater evidence of mycobacterial CNS-IRIS may emerge as ART increases in availability worldwide. If a patient presents with clinical deterioration and meningeal enhancement on MRI or communicating hydrocephalus

in the context of ART initiation with adequate treatment for mycobacteria, IRIS should be strongly considered in the differential diagnosis.

Parasitic Pathogens

Parasitic infections have not been found to contribute significantly to CNS-IRIS in patients with HIV infection. Several cases of toxoplasmosis-associated CNS-IRIS have been described, manifest as encephalitis[66]; in one case elevated CD8+ T-cell infiltrates were found in the CNS tissue.[67] As parasitic infections have greatest morbidity in resource-limited settings, recognition may be challenging without access to neuroimaging; similarly, prevalence may be increasing with greater availability of ART.

Management of Opportunistic Infection–Related CNS Immune Reconstitution Inflammatory Syndrome

Challenges in management. Since the various clinical scenarios of HIV CNS-IRIS are characterized by different OIs, no single treatment modality can reverse the detrimental immune response. In the case of CNS-IRIS following ART initiation in patients with HIV infection, the best therapy is prevention. The greatest predictor of whether an HIV-infected patient will develop IRIS is the CD4 nadir[68]; therefore, if HIV is detected and treatment initiated early in the disease course, CNS-IRIS is less likely to develop. While no immune-specific therapy exists, discovering as much as possible regarding the presence of opportunistic organisms in the immunocompromised patient may help guide treatment decisions. In HIV-infected patients with known OIs, delaying ART in certain circumstances while the infection is treated has shown benefit, although this has not been reproduced consistently and may be etiology specific. In patients in whom treatment with ART cannot be delayed who are receiving treatment for OIs, steroids may also be used, although little evidence exists to guide physicians in this recommendation. Steroids are most often used in cases of profound immunodeficiency, such as PML, in which no effective antimicrobial treatment is available for the infection(s) present and increasing inflammation related to IRIS presents the risk of herniation or vascular compromise. While no large trials have been done on which to base these treatment decisions, reports have recently been published regarding which subpopulations are more or less likely to benefit from high-dose steroids in IRIS.[69]

In the absence of randomized treatment trials, management of patients with HIV infection who develop CNS-IRIS after initiating ART must be guided by the nature of the underlying infection, the acuity of the clinical presentation, and the tolerability of corticosteroids.

Antiretroviral therapy. Because a low CD4+ T-cell nadir remains the most consistently identified predictor of the development of CNS-IRIS, early diagnosis and early intervention with ART continue to be paramount in importance. In one study in which patients were started on ART when CD4+ T-cell counts were above 400, the incidence of IRIS was 8%, significantly lower than what has been traditionally reported in the literature.[70] ART may be delayed, however, when an HIV-infected patient has a known underlying OI for which effective antimicrobial treatment is available. The optimal timing of delayed ART initiation is unclear. In one study of cryptococcal meningitis, delaying ART for up to 1 month while antifungal therapy was given improved outcomes.[71] In a study of severely immunocompromised patients in Cambodia (CD4+ T-cell count less than 200 with a mean of 25 cells/μL), delaying ART for only 2 weeks instead of 8 weeks during antituberculosis therapy

KEY POINT

- Early diagnosis in the HIV disease course and early intervention with antiretroviral therapy are the best ways to prevent CNS immune reconstitution inflammatory syndrome. There is a rationale for delaying antiretroviral therapy in patients with an underlying opportunistic infection while the infection is treated.

KEY POINTS

- High-dose corticosteroids are required in patients with immune reconstitution inflammatory syndrome in whom brain herniation is impending but may also be helpful in less dire situations when patients are symptomatic from CNS immune reconstitution inflammatory syndrome.
- CNS immune reconstitution inflammatory syndrome may exist without an identifiable underlying opportunistic infection, in which case the CD8+ T cells may be attacking viral reservoirs within the brain, or the brain itself. These syndromes are usually manifest as fulminant encephalitis with white matter changes on MRI.

reduced mortality by 34%.[72] Thus delaying ART is recommended over discontinuing ART once it has been initiated, as stopping therapy increases the risk for drug resistance and disease progression.

Immunomodulatory therapy. In HIV-infected patients with CNS-IRIS due to OI in whom massive inflammation has resulted in impending herniation, high-dose corticosteroids are required.[73] We prefer 1 g/d of methylprednisolone IV, or an equivalent dose of any other corticosteroid, for 5 days with a gradual taper over 4 to 6 weeks. While reasonable concern exists about the complications of further immunosuppression in these patients, it is our experience that stopping steroids after 3 to 5 days will often lead to recurrence of IRIS symptoms. This may be explained by rebound of cytotoxic T cells in response to the underlying OI once steroids have been removed. When effective antimicrobial therapy exists for the underlying OI, steroids may not be necessary for such a prolonged duration since the infection may respond to treatment. In cases such as CNS-IRIS due to PML, steroids may be required for a prolonged time until memory T cells recover and can mount a response to JC virus, usually within 4 to 6 weeks.[55] Such prolonged use of steroids requires prophylaxis for pneumocystis pneumonia and fungal infections, and for tuberculosis in endemic regions.

In HIV-infected patients with CNS-IRIS due to OI who are symptomatic but without impending brain herniation, the use of corticosteroids is far more controversial. While modulating the immune response to an underlying infection may seem at odds with the goal of clearing the infection, evidence suggests that the immune response in these patients is dysfunctional or in excess of what is required to control the infection. Historically, IRIS-related syndromes such as the leprosy reaction have been treated with adjunctive corticosteroid therapy; the efficacy of this treatment has been demonstrated in clinical trials. Without careful prospective trials in CNS-IRIS, physicians must use their own clinical judgment in the context of each symptom and OI. In *Cryptococcus*-related CNS-IRIS, steroids may be helpful in concert with CSF drainage when inflammation leads to obstruction of CSF pathways and intracranial hypertension.[74] In HIV-infected patients with CNS-IRIS as demonstrated by enhancement on MRI without clinical symptoms, the risk to benefit ratio is unlikely to favor steroid treatment.

HIV CNS–Immune Reconstitution Inflammatory Syndrome Without Opportunistic Infection

During immune reconstitution, patients with HIV infection are at risk for other disease manifestations of IRIS unrelated to underlying infection. These noninfectious IRIS syndromes range from fulminant encephalitis to chronic syndromes such as autoimmune disease in HIV.

Fulminant HIV encephalitis with immune reconstitution inflammatory syndrome. Initiation of ART has resulted in severe, progressive encephalitis in some patients with HIV infection. Series of patients have been described with either worsening of preexisting encephalitis or dementia, or the new development of such after initiation of ART.[74] The clinical deterioration in mental status in these patients may be accompanied by leukoencephalopathy on MRI, with involvement of the uncinate fibers. The histopathologic correlate shows a mass inflammatory infiltrate made up of predominantly CD8+ T cells in perivascular regions as well as the parenchyma, in the absence of any detectable pathogen. CD8+ T cells have been

found immediately adjacent to neurons in HIV encephalitis, implicating cytotoxic T cells in neuronal toxicity.[75] Alternatively, an HIV-infected patient with encephalitis after ART has been described with a fulminant focal area

Case 4-3

A 59-year-old man with newly diagnosed HIV infection had a CD4+ T-cell count of 37 cells/μL and an HIV viral load of 95,710 copies/mL. Six days after initiation of ART, he developed an acute onset of profound encephalopathy. He had a transcortical sensory aphasia, prolonged speech latency, apraxia, and diffuse, small amplitude myoclonus. MRI of the brain showed the new development of symmetric areas of abnormal T2/FLAIR signal in the medial temporal lobes, extending into the subinsular white matter on the left, with subtle enhancement present in the left subinsula, increased vascular markings in the right basal ganglia, and diffuse dural enhancement from a lumbar puncture (**Figure 4-3**). CSF showed 3 WBCs/μL, normal glucose concentration, and protein concentration elevated at 80 mg/dL. The CSF test results were negative on flow cytometry and cytology, as well as for cultures for bacteria, fungi, and mycobacteria; PCRs for cytomegalovirus, Epstein-Barr virus, herpes simplex virus, human herpesvirus 6 and 7, JC virus, and VZV were also negative. His serum showed slightly elevated ammonia at 53, normal thyroid function test, and B_{12} level of 993. His HIV viral load had fallen to 2858 copies/mL on the day of his mental status change. Over several days his mental status worsened and he was barely responsive to stimuli. High-dose corticosteroids (dexamethasone 10 mg twice daily) were started, with improvement in his speech and apraxia in the first 24 to 36 hours. Within 6 days he was close to his prior baseline and several weeks later was able to be discharged to home on a gradual taper of corticosteroids.

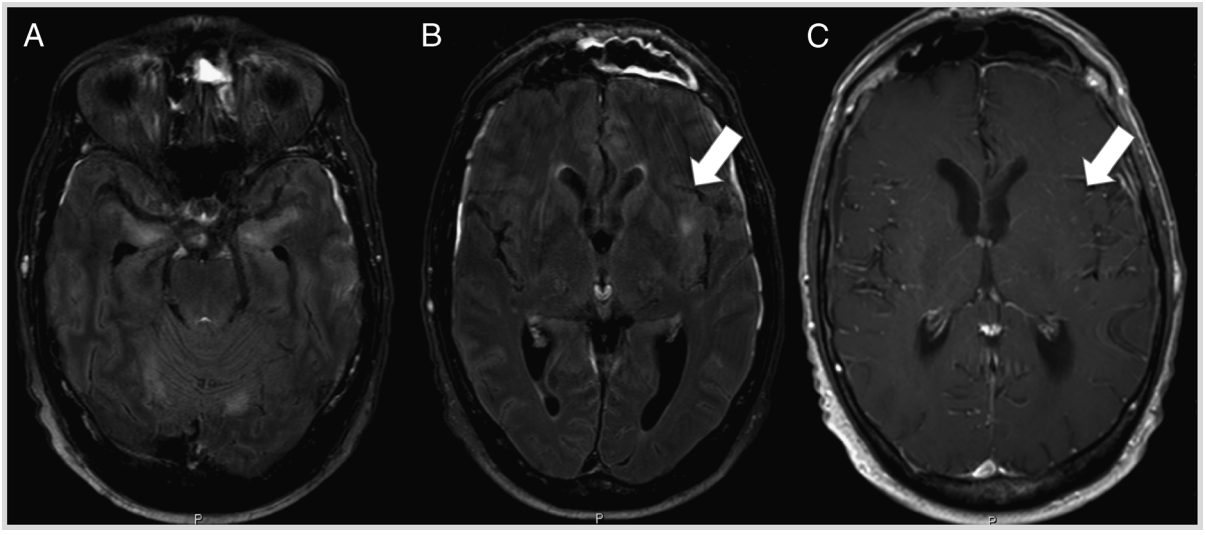

FIGURE 4-3 Fluid-attenuated inversion recovery (*A*, *B*) and T1 postgadolinium (*C*) sequences of MRI show hyperintense signal in the bilateral mesial temporal cortex (*A*) and the periventricular white matter of the left subinsular cortex (*arrow*, *B*). The signal abnormality in the left subinsular cortex is found to have very subtle enhancement on the postgadolinium image. Increased vascular markings are also seen in the right basal ganglia (*arrow*, *C*). While the enhancement is subtle, early intervention with corticosteroids reversed the encephalopathy in this case, providing further evidence that early inflammation was developing.

Comment. While no opportunistic organism could be identified as the etiology of his mental status change, this patient was at risk for IRIS given his low CD4+ T-cell count at the time of initiation of ART, as well as the rapid decrease in his HIV viral load after starting ART. The enhancement on MRI, albeit subtle, also provided a clue to the diagnosis. In a patient with clinical deterioration in the context of improved virologic control, the diagnosis of IRIS, and therefore treatment with adequate doses of immunomodulatory agents, must be considered.

of demyelination or tumefactive inflammation, similar to the Marburg variant of multiple sclerosis.[76] The focal nature of this patient's presentation invokes the question of whether, in the absence of any pathogen, T cells are targeted against the viral reservoirs in the brain or the brain itself, and whether the nature of the encephalitis, focal or widespread, might imply different disease mechanisms. Corticosteroids have been used in HIV-infected patients with noninfectious encephalitis after ART initiation, sometimes with dramatic improvement in clinical status (**Case 4-3**).[74]

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